Working Title: The causal role of left and right superior temporal gyri in speech perception in noise, a TMS study

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Abstract

Successful perception of speech in everyday listening conditions requires effective listening strategies to overcome common acoustic distortions such as background noise. Convergent evidence from neuroimaging and clinical studies identify activation within the temporal lobes as key to successful speech perception. However, current neurobiological models disagree on whether the left temporal lobe is sufficient for successful speech perception or whether bilateral processing is required. We addressed this issue using Transcranial Magnetic Stimulation (TMS) to selectively disrupt processing in either the left or right superior temporal gyri (STG) of healthy participants to test whether the left temporal lobe is sufficient or whether both left and right STG are essential. Participants repeated keywords from sentences presented in background noise in a speech reception threshold task while receiving online repetitive TMS separately to left STG, right STG, vertex, or while receiving no TMS. Results show an equal drop in performance following application of TMS to either left or right STG during the task. A separate group of participants performed a visual discrimination threshold task to control for the confounding side effects of TMS. Results show no effect of TMS on the control task, supporting the notion that the results of experiment 1 can be attributed to modulation of cortical functioning in STG rather than to side effects associated with online TMS. These results indicate that successful speech perception in everyday listening conditions requires both left and right STG and thus have ramifications for our understanding of the neural organisation of spoken language processing.

Keywords:

Transcranial Magnetic Stimulation; Speech Perception; Sentence processing; Auditory Cortex; Superior Temporal Gyrus.

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Since the initial observations of Carl Wernicke in 1874 that the posterior superior temporal gyrus must be the sensory speech centre of the brain, the notion that Wernicke's area is the neural locus of auditory speech processing has become one of the most widely accepted concepts in cognitive neuroscience. Despite the intervening years, fundamental questions relating to the neurobiology of speech perception still exist such as how exactly the two hemispheres contribute to speech perception. Two prominent neurobiological models of speech perception are the unilateral model of Rauschecker and Scott (2009) and the bilateral model of Hickok and Poeppel (2000). Both build on the notion that speech perception occurs in the context of a dual stream of processing with a ventral pathway involved in mapping sound to meaning and a dorsal pathway mapping sound to articulatory motor processes. Rauschecker and Scott (2009) argue that *"…speech perception and production are left lateralised in the human brain."* (p. 720) with the locus of successful speech perception in the left anterior superior temporal gyrus (STG) (Rosen, Wise, Chadha, Conway, & Scott, 2011; Scott, Blank, Rosen, & Wise, 2000). In contrast, Hickok and Poeppel (2000) argue that speech perception is processed bilaterally and propose the existence of a speech perception pathway in each hemisphere capable of processing speech sounds up to and including the mental lexicon (Hickok & Poeppel, 2007). Moreover, effective speech perception is thought to rely on sites both anterior and posterior of the transverse temporal gyrus, with phonological processing especially occurring bilaterally and semantic processing being more left dominant (Hickok, 2009).

The argument in favour of bilateral speech perception comes mainly from patient data where unilateral lesions or unilateral anaesthetisation during WADA testing of either the left *or* right hemisphere (Hickok et al., 2008; McGlone, 1984) partially impairs speech perception. In contrast, patients with bilateral lesions encompassing both left *and* right superior temporal regions are more likely to suffer from verbal auditory agnosia, an inability to understand spoken language despite preservation of other language capabilities, i.e. reading or writing (Buchman, Garron, Trost-Cardamone, Wichter, & Schwartz, 1986). Out of the 63 well-detailed cases of verbal auditory agnosia there were ~70% with bilateral lesions, supporting the notion that both left and right hemispheres are critical to speech perception. Yet the remaining 30% had unilateral damage (only one patient had a right hemisphere lesion) and still had auditory agnosia (Slevc & Shell, 2015), suggesting that the left STG may be sufficient for speech recognition. Results from patient data are, therefore, inconclusive with respect to the unilateral or bilateral organisation of speech processing. The damage caused by lesions or strokes, however, is not constrained to functional or anatomical boundaries. Furthermore, the neuroplastic changes and reorganisation that occur after brain injury make it difficult to localise the specific origin of the resultant cognitive deficit.

Whilst such issues can be overcome by investigating the neural processing of healthy human participants, neuroimaging studies have thus far also reported mixed results with respect to the question of whether speech processing occurs uni- or bilaterally. Several neuroimaging studies on processing of intelligible speech report a left-lateralised locus of processing (Binder et al., 1997; Evans & McGettigan, 2017; Evans, McGettigan, Agnew, Rosen, & Scott, 2016; McGettigan et al., 2012; Narain et al., 2003; Scott et al., 2000), while later studies have reported bilateral involvement of temporal areas in speech perception (Evans et al., 2014; Friederici, Kotz, Scott, & Obleser, 2010; Harris, Dubno, Keren, Ahlstrom, & Eckert, 2009; Obleser, Eisner, & Kotz, 2008; Okada et al., 2010; Rosen et al., 2011; Zekveld, Heslenfeld, Festen, & Schoonhoven, 2006). It is likely that the lack of consistency with respect to the laterality of STG involvement during speech is not only due to methodological differences between studies, but also due to the correlational nature of such methods where observed changes in the blood oxygen level dependent signal can either be functionally relevant or epiphenomenal.

Transcranial Magnetic Stimulation (TMS) is a neurophysiologic technique that allows for non-invasive stimulation of the human brain through the application of strong but short magnetic pulses that enable us to modulate the underlying neural activity in conscious, healthy human subjects (non-invasively). By inducing electrical currents in the brain that modulate and disrupt the ongoing activation within a given region, TMS can be used to demonstrate causality between a cognitive process and specific brain regions. As a result, TMS can be used to complement other neuropsychological techniques (such as fMRI and EEG), which are correlational in nature (Paus, 2005; Sack, 2006). Given the potential for causal conclusions, TMS is a valuable method to study the neurobiology of speech perception (Adank, Nuttall, & Kennedy-Higgins, 2017). It is perhaps surprising that few studies have been published in this research area.

Thus far, TMS has been found to impair both semantic and phonological judgments after left posterior superior temporal gyrus stimulation (Krieger-Redwood, Gaskell, Lindsay, & Jefferies, 2013) as well as prosodic judgments (Alba-Ferrara, Ellison, & Mitchell, 2012) and human voice perception after right posterior superior temporal gyrus stimulation (Bestelmeyer, Belin, & Grosbras, 2011). Given the critical importance of these regions in speech perception, it is perhaps not surprising that the application of TMS disrupted performance across these studies. Krieger-Redwood et al. (2013) conclude that the impairment is the result of TMS increasing the “ambiguity of the auditory input to the system which necessarily impacts on processing at all levels” (p.2185). Taken together, this research suggests that TMS can be used to further our understanding in a way that complements other research techniques.

Yet, TMS also has limitations that need to be considered before adopting it as a viable technique. The most referred to concept in TMS research is the creation of a 'virtual lesion' (Pascual-Leone, Bartres-Faz, & Keenan, 1999). A common misunderstanding of this phrase is that the induced 'virtual lesion' results in a complete loss of cognitive ability within the region being stimulated, i.e., TMS is capable of inducing deficits akin to cortical deafness. Whilst some such effects have been observed in a limited fashion within the visual system (Amassian et al., 1989), generally the effects in other cortical regions are far more subtle, and experiments rely on more fine-grained distinctions in performance across tasks/stimulation sites shown through reaction times, error rates, or motor evoked potentials. This is a general property of TMS rather than specific to neurobiology of language research; however, it must be considered when assessing the research conducted so far. Meister, Wilson, Deblieck, Wu, and Iacoboni (2007) found no effect on discrimination of two consonant-vowel syllables in noise after left STG stimulation despite finding an impairment of tone discrimination and Drager, Breitenstein, Helmke, Kamping, and Knecht (2004) found no effect relative to baseline in a picture-word verification task. Whilst Beauchamp, Nath, and Pasalar (2010) found that subjects were significantly less likely to report a McGurk effect after single pulse TMS to STG. They conclude that this result is best explained as interfering with audio-visual integration rather than as evidence that TMS can interfere with speech perception. Thus, whilst TMS does provide the opportunity to establish causal brain-behaviour links, the very subtle effect that TMS has on the overall network makes the task of establishing causal relations far more complex, especially within a network that is as highly redundant as the speech perception network (Price & Friston, 2002). Indeed, Meister et al. (2007) theorise that the network for speech perception within the temporal lobes is too extensive to be compromised by TMS "because of compensatory processes within the contralateral temporal cortex" (p.1695).

The view that it is challenging to disrupt speech perception by targeting a single area using TMS is supported by Andoh and Paus (2011). They combined 1Hz offline repetitive TMS with functional imaging to investigate the impact that stimulating the superior temporal region of each hemisphere would have on activation in the contralateral hemisphere. The results showed a task-related increase in activation in the homologue areas contralateral to the site of stimulation, i.e., stimulation of the left posterior temporal region resulted in a task-related increase in activation in the right superior and middle temporal gyri and the left cerebellum. Andoh and Paus (2011) suggest that these results are evidence of the brain compensating for the TMS-induced disruption to one hemisphere by drawing on additional resources from the opposite hemisphere. The authors suggest that this interhemispheric compensatory process is the reason why behavioural effects are not always observed after application of TMS. Moreover, they argue that this interhemispheric compensation is likely to represent the early stages of reorganisation that occur in patients following neurological trauma, with individual differences in the degree of interhemispheric compensation explaining the variable impact of unilateral or bilateral damage.

The aim of the current study was to evaluate claims regarding the involvement of the superior temporal gyrus made by the neurobiological models of Rauschecker and Scott (2009) and Hickok and Poeppel (2000) by using repetitive TMS to temporarily and selectively disrupt processing in either the left *or* right hemispheres of healthy human subjects and measure the effect on participants' speech perception. Participants' ability to perceive speech in noise was assessed by comparing their performance on a speech reception threshold (SRT) task (Plomp & Mimpen, 1979a, 1979b) without TMS (control condition) and while receiving TMS separately to the left STG, right STG (experimental sites) or vertex (control site). In experiment 1, we emulated everyday listening conditions by presenting participants with spoken sentences embedded in background noise. The bilateral model of Hickok and Poeppel (2000) predicts that TMS to left or to right STG will result in poorer performance relative to no TMS, while the unilateral model of Rauschecker and Scott (2009) predicts that only rTMS to left STG should impair performance, with no effect of right STG stimulation. Experiment 2 replicated the TMS parameters of experiment 1, but involved the use of a non-speech, visual discrimination task in place of the speech reception threshold task of experiment 1. This is a task that does not engage the STG of either hemisphere and was therefore included to test whether the results from experiment 1 could be explained by nonspecific side effects of rTMS, e.g., the distraction that arises from facial twitching. Following Andoh and Paus (2011), the current study adopted an online rTMS paradigm to maximise cortical modulation within the STG whilst minimising the possibility of interhemispheric compensation reducing or eliminating the behavioural effects of the stimulation.

Experiment 1

Methods

Participants

Sixteen participants took part in this study (18-41 years old; mean 23.25 years; SD 6.94; 11 females). All participants were native British English speakers, with no reported history of speech, language, neurological or psychiatric disorders. Hearing thresholds were not explicitly measured; however all participants reported no history of hearing difficulty, the stimuli were presented suprathreshold (i.e. at a level higher than 20dB HL) and no participant showed any sign of potential hearing difficulty in the baseline no TMS condition i.e. all participants performed within the expected range. All were safety screened according to UCL's protocols and presented no contraindications to either MRI or TMS. All participants gave informed written consent for both the MRI and TMS test sessions with all sessions approved by the University research ethics committee (#0599/001). Participants were paid or received course credit.

Procedure

Participants' ability to perceive speech in noise was assessed by comparing their performance on the speech reception threshold task (Plomp & Mimpen, 1979a, 1979b). All sentences occurred in the presence of speech-shaped noise with the signal to noise ratio (SNR) varying adaptively depending on individual participant performance. The first sentence was presented at a favourable SNR, for example +20dB. Correct repetition of three or more keywords resulted in a reduction of 10dB on subsequent trials, until participants were unable to correctly repeat more than two keywords. At this point the SNR increased in steps of 6dB until another reversal occurred with all subsequent changes occurring in steps of 4dB. In all cases the level of the speech signal remained constant, with the noise file varying in intensity. A reversal refers to the shift in direction of SNR change from one trial to the next, for example, if a participant repeated more than three keywords for four sentences in a row, then the SNR will reduce after each sentence making the subsequent sentence on each occasion harder to perceive. If on the fifth sentence the participant was unable to repeat at least three of the keywords, the SNR will increase making the subsequent sixth trial easier to understand. Such a change in direction from decreasing to increasing (or vice versa) SNR represents a reversal. Participants' speech reception thresholds were computed by taking the mean SNR from all trials where a reversal occurred (Plomp & Mimpen, 1979a, 1979b; Schoof & Rosen, 2014).

After presentation of each sentence, participants were asked to repeat verbatim what they heard. Responses were scored online immediately after each trial using a graphical user interface on a standard computer screen that was not visible to participants. Each sentence contained five keywords upon which scoring was based, for example: “The MEAL was COOKED BEFORE the BELL RANG” (keywords in uppercase letters). Keywords were also judged to be correct if participants changed the grammatical number of presented words e.g. ‘Meal**s**’ (plural) instead of ‘Meal’ (singular). All other variations were scored as incorrect with no feedback given. Scoring of all responses was performed by the same author (P.A.). There was no inter-judge reliability measure. It is for this reason that the scoring occurred under the very strict parameters outlined above i.e. only changes in number were permitted all other errors were scored as incorrect. Where the participant did not respond clearly, the scorer asked them to repeat their response.

Orders of sentence list were counterbalanced using a Latin-square technique. All sentences were pseudo-randomly ordered such that the order of presentation was different between participants, but each sentence was only played once per participant.

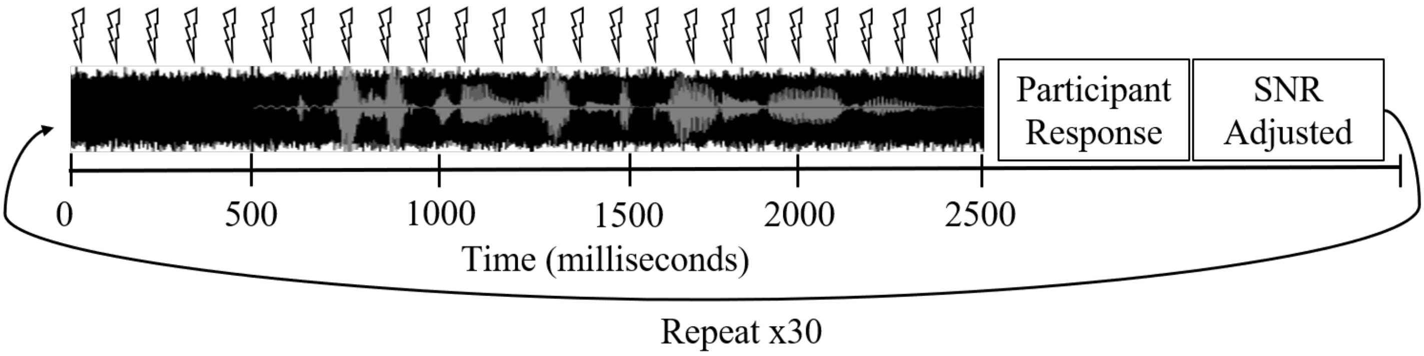

Figure 1- Illustrating the timing of events on an average speech reception threshold trial. Repetitive TMS and noise (represented by lightning bolts and black broadband waveform respectively) start 500ms before the onset of the target sentence (represented by the grey waveform). Repetitive TMS, noise and target sentence offsets all occurred concurrently.

Stimuli

Four lists of 30 sentences were created from a pre-recorded set of the Institute of Electrical and Electronical Engineers (IEEE) sentences (IEEE, 1969). Some sentences were adapted from the original American English to suit the native British English sample of participants e.g. *"The hogs were fed chopped corn and garbage"* was adapted to *"The pigs were fed chopped corn and rubbish"*. One male speaker of standard southern British English read all sentences in a sound attenuated room, the stimuli were original recorded by Rosen, Souza, Ekelund, and Majeed (2013). Audio digitising was performed at 44.1kHz and 16 bits. The beginning and end of each sentence was trimmed to zero crossings as closely as possible to the onset/offset of the initial and final speech sounds. The sentences were then peak-normalised to 99 percent of maximum amplitude and scaled to 70dB sound pressure level using Praat (Boersma & Weenink, 2014). Sentences were presented in steady state speech-shaped noise the spectrum of which was derived from the 120 test sentences without amplitude modulation; on all trials, the noise masker started 500 milliseconds before the onset of the sentence with the noise, sentence and TMS offsets all occurring concurrently. All sentences were presented binaurally via Etymotic ER1 earphones using a custom-made MATLAB script (R2013a; The Mathworks Inc., Natick, MA).

Transcranial Magnetic Stimulation

Stimulation was performed using a Magstim Rapid^2 and a 70mm figure-of-eight coil (Magstim, Whitland, UK). Pulses were delivered online (i.e., during sentence presentation) at a rate of 10Hz for 2500 milliseconds, starting 500 milliseconds before each sentence began and continuing until the sentence had finished (25 pulses per trial). 10Hz stimulation has previously been shown to be effective at disrupting processing within superior temporal regions (Andoh & Paus, 2011; Bestelmeyer, Belin, & Grosbras, 2011; Bueti, van Dongen, & Walsh, 2008; Pitcher, 2014). The longest sentence was 2500 milliseconds in length and thus 25 pulses were chosen in order to ensure that TMS was applied throughout the entire length of all sentences. Stimulation intensity was set at 40% of maximum stimulator output and held constant across all participants. During a period of extensive pilot testing, it was found that 40 percent of maximum stimulator output was found to be of sufficient intensity to have an experimental effect without causing significant discomfort for the participants. Additionally, the 40% stimulation intensity was sufficiently low to prevent the coil from overheating, thus ensuring that we did not need to switch coils between conditions. Motor thresholds were not used as their applicability to non-motor regions is yet to be fully established (Stewart, Walsh, & Rothwell, 2001; Stokes et al., 2013) and previous experiments employing a similar methodology to the present experiment have shown that the use of single threshold can be effective in the superior temporal region (Bueti et al., 2008; Pitcher, 2014). The TMS frequency, intensity, and duration were well within established international safety limits (Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Wassermann, 1998)

Prior to the main experiment, all participants received three to four trains of pulses per site, to ensure they were comfortable with the stimulation parameters. During this demonstration, all participants used an earplug (3M E.A.R., 36dB attenuation) in the ear ipsilateral to the site of stimulation to attenuate the sound of the coil discharge and avoid damage to the ear (Counter, Borg, & Lofqvist, 1991). During the main experiment, magnetically shielded ER1 Etymotic earphones were used bilaterally, to deliver the auditory stimuli and to attenuate the sound of coil discharge.

Test of Etymotic ER1 earphones

Prior to the main experiment, a pilot test of the attenuation capabilities of the ER1 earphones was conducted to investigate whether the acoustic click of the TMS coil interferes with the main experimental task. A B&K 4157 coupler was used (Brüel & Kjær sound and vibration measurement, Nærum, Denmark) with the output connected to the left channel of a Scarlett 2i2 USB interface (Focusrite Audio Engineering Ltd, High Wycombe, U.K.). The Scarlett 2i2

USB interface was adjusted such that with the ER1 not inserted into the coupler and the Magstim rapid2 (Magstim, Carmarthenshire, U.K.) module running at 10Hz, 100 percent maximum intensity (i.e., the 4157 responding to the acoustic click from the TMS coil) the recorded level was about six decibels below overload. The ER1 inputs were connected to 50ohm terminators, and only the right channel ER1 was used for the measurements, which were recorded using cooledit 96 (Adobe systems, Inc., San Jose, USA) at a sampling rate of 44.1kHz, 16 bit.

A 70mm diameter figure-of-eight TMS coil was held approximately 30cm above the ER1 shielded transducer box. With the ER1 not inserted into the coupler the Magstim rapid2 module was run at a rate of 10Hz, 100 percent of maximum pulse strength. Under these conditions, the acoustic click associated with firing the TMS coil was recorded at a level of 81.9 dB SPL. Then, in order to assess the acoustic leakage through the foam insert of the ER1 earphones, with the TMS coil held in the same position, the ER1 was inserted into the B&K coupler and the Rapid2 module was again run at 10Hz, 100 percent maximum stimulator output. Under these conditions, the acoustic click of the TMS coil was recorded at 37.8 dB SPL, inferring an attenuation of 44.1 dB, resulting in a level of background noise that was believed to be low enough to not impact upon the main experimental task. This conclusion was confirmed anecdotally when all participants reported being able to comfortably hear the sentences over the noise of the TMS pulses with no noticeable difference compared to the vertex stimulation condition.

MRI scanning

Participants came to the Birkbeck-UCL Centre for Neuroimaging (BUCNI) to get a T1-weighted structural magnetic resonance imaging scan. [FLASH sequence, repetition time (TR) = 12ms, echo time (TE) = 5.6ms, flip angle = 19°, resolution 1mm x 1mm x 1mm].

Immediately after the scanning session, the individual MRI slices were processed to create one composite image and rotated to match the orientation of the MNI 152 template brain. During the TMS session, the structural scan was used in conjunction with BrainSight frameless stereotaxy (Rogue Research, Montreal, Canada). BrainSight uses an infrared camera and tracking system and displays the specific location and orientation of the TMS coil in real time on the individual participants MRI ensuring accurate and consistent stimulation of the target and control site.

The experimental sites for this study were taken from Adank (2012), who conducted an Activation Likelihood Estimation (ALE) meta-analysis of 57 fMRI and PET studies that contrasted intelligible with less intelligible or unintelligible speech stimuli. ALE is used to establish the degree of overlap between coordinates taken from different neuroimaging papers. Across all 57 studies the site with the highest ALE score and therefore the site with the most observed activation across studies was the left anterior superior temporal sulcus with MNI coordinates of x= –60, y= –12, z= –6. A less active homologous cluster was found in the right anterior superior temporal sulcus (x= +62, y= –8, z= –10). These two sets of coordinates were used as guides for placement of the TMS coil. In some participants these coordinates did not match up to the superior temporal sulcus, therefore small visually guided adjustments of the coordinates were made on a participant-by-participant basis to ensure that stimulation targeted the STG across all participants, in all cases the smallest possible adjustment to the y-coordinate was made with the x and z coordinates held consistent with those adopted from Adank (2012). Average MNI coordinates of target sites within the final sample in experiment 1 for the left STG were x= –60, y= –12, z= –6 and the right STG were x= +61, y= –8, z= –10. Vertex was used as a control site and was identified as the highest point of the skull in the midsagittal plane.

Data Analysis

The dependent variable for the speech reception task in all experiments is the average SNR level at which reversals occurred across the 30 test sentences per condition. A one-way repeated-measures analysis of variance (ANOVA) was conducted to investigate the effect of TMS condition on performance for each experiment separately. The within-subjects factor is stimulation type (no TMS vs vertex vs left STG vs. right STG). In experiment 1, all data was normally distributed according to Shapiro-Wilk test of normality (all p's >.2). In experiment 2, two conditions were shown to be non-normally distributed (left STG, p = .006 and no TMS, p = .004). Despite two of the conditions being non-normally distributed in experiment 2, for ease of comparison between experiments the results of the one-way ANOVA are reported below. This is because this type of ANOVA is robust to deviations in normality (Glass, Peckham, & Sanders, 1972; Lix, Keselman, & Keselman, 1996) and the results of the non-parametric Friedman test were equivalent to the one-way ANOVA. All scores for both experiments fall within three standard deviations of the mean and therefore no score was considered to be an outlier. Bonferroni-corrected paired samples *t*-tests were used for all follow-up analyses.

Results

A repeated-measures analysis of variance (ANOVA) was conducted to investigate whether the application of TMS to different anatomical landmarks (no TMS; vertex; left STG; right STG) would produce differential effects on participants' ability to perceive speech in noise. Due to the functional relevance of bilateral STG in speech perception, overall thresholds were expected to be higher, representing poorer performance, after separate application of TMS to both the left and right STG conditions relative to the no TMS and vertex control conditions. A significant main effect of TMS location was found $F(3,45)=10.47$, $p<.001$, $\eta^2=0.41$, indicating that TMS had a differential effect on speech perception ability depending on location of stimulation. Post-hoc paired samples *t*-tests confirmed that stimulation of left (M -1.64dB ± 1.61) and right STG (M -0.99dB ± 1.81) impaired perception of sentences presented in noise relative to both the no TMS (M -2.96dB ± 1.57) and vertex (M -2.81dB ± 1.67) stimulation conditions (see Table 1 for all relevant statistics). No difference was observed between either of the control conditions or between performance in the left and right STG stimulation conditions (see Figure 2). Therefore, TMS was more disruptive when stimulation was applied to either left or right STG compared to the vertex or no stimulation conditions.

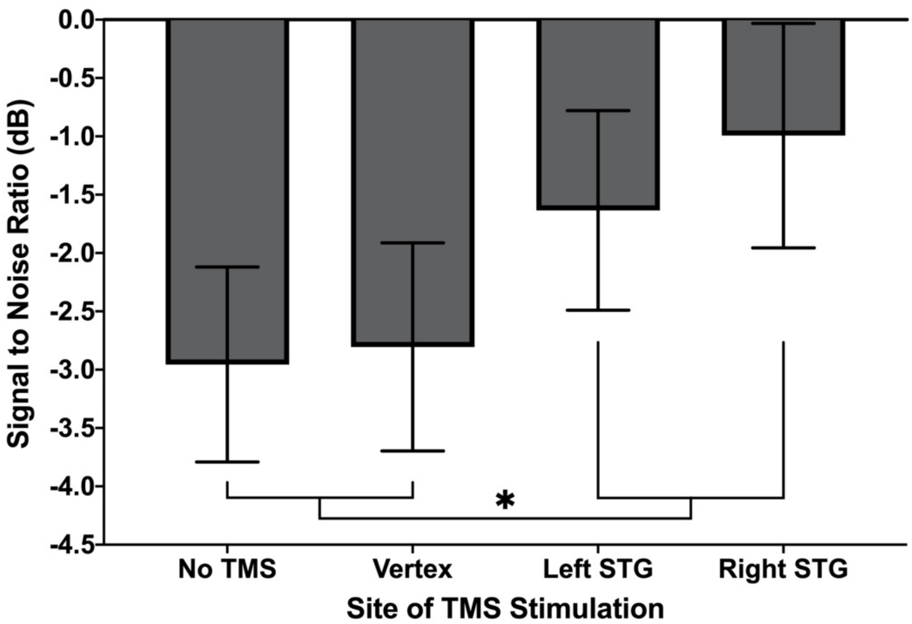

Figure 2 - Depicting the average signal to noise ratio level at the point of a reversal across the four sites of TMS stimulation. Error bars represent 95% confidence intervals. * = p<.01

Table 1 - Summary of the pairwise comparison statistics for experiment 1.

Site A	Site B	*t*	*p*	Mean Difference	Confidence Interval of mean difference	Cohen's *d*
L STG	R STG	-1.30	.213	-0.64	[-1.69, 0.4]	-0.325
L STG	No TMS	3.12	.007	1.32	[0.41, 2.22]	0.78
L STG	Vertex	3.64	.002	1.17	[0.48, 1.85]	0.91
R STG	No TMS	4.57	<.001	1.96	[1.04, 2.87]	1.14
R STG	Vertex	4.19	.001	1.81	[0.89, 2.73]	1.04
No TMS	Vertex	-0.42	.676	-0.15	[-0.9, 0.6]	-0.105

Notes: Bonferroni corrected alpha-level = (.05/6) = .008

Interim Discussion

Speech reception thresholds were found to be elevated, reflecting poorer performance as participants required a more favourable SNR in order to perform at an equivalent level, after application of online repetitive TMS to either left or right superior temporal gyri compared to a no TMS control condition and the TMS control site (vertex). These results are important as the equal drop in performance across the left and right STG stimulation conditions supports accounts that propose bilateral processing in speech perception.

TMS research paradigms usually incorporate a stimulation control site, i.e., a site that is stimulated despite its lack of functional relevance to the task/behaviour under investigation. This is to ensure that any observed changes in behaviour are caused by the intended disruption of cortical processing at the main experimental site and are not caused by general changes in attention/arousal caused by the TMS click and/or skin sensations that occur every time a TMS pulse is delivered. One alternative explanation for the results observed in experiment 1 could be that the TMS coil was closer to the ears in both STG conditions compared to the vertex condition. As a result, therefore the acoustic noise of discharging the coil (the click) was potentially more intense and therefore more disruptive, independent of the effect on the underlying neuroanatomy. This explanation is precluded however, by the fact that, prior to experiment 1 the Etymotic ER-1 earphones were tested and showed a good level of attenuation of the TMS coil click resulting in a level of background noise that was believed to be low enough to not impact upon the main experimental task. Furthermore, after data collection, the anecdotal responses from participants indicated no difficulty in hearing the speech stimuli in either of the experimental conditions compared to the control conditions, thus supporting our view that the results observed in experiment 1 are not confounded by potential differences in the acoustic intensity of the TMS coil click across conditions.

Acoustic noise, however, is only one non-specific effect of stimulation, the validity of the current results could be questioned, as the application of TMS directly innervated the temporalis muscles and thus caused a twitch in the canthus of the eye and the jaw of all participants. These twitches can at times be distracting and uncomfortable (Duecker & Sack, 2015). Because this facial twitching does not occur during vertex stimulation, it is possible that participants were simply more distracted by TMS in the left and right STG stimulation conditions during stimulus presentation compared to the control site stimulation. In order to test whether the results of the first experiment could be explained solely in terms of these non-specific TMS distractions, a follow-up experiment was conducted where participants completed a visual discrimination threshold task under the same four TMS conditions used in experiment 1 (left STG; right STG; vertex; no TMS). A visual discrimination threshold task was used because the bilateral superior temporal gyri are likely to be functionally irrelevant to this visual task. Therefore, if a disruptive effect of TMS location is found, it suggests that the observed effects of experiment 1 are due to the confounding side effects of TMS application (e.g. the distraction that arises from facial twitches). In contrast, if no effect of

TMS was found in experiment 2, it would support the notion that the results of experiment 1 were evidence of bilateral STG involvement in speech recognition.

Experiment 2

Methods

Participants

Seventeen participants took part in this study, all of whom met the same eligibility criteria as outlined in experiment 1 and who were paid for their participation. In addition to the previously outlined eligibility criteria (i.e. native British English, right-handed, with no reported history of speech, language, neurological or psychiatric disorder), the participants' visual acuity was assessed to establish if it was within the normal range. All participants were assessed to have a binocular vision rating of less than 0.1 on the LogMAR scale equating to greater than 0.8 on the decimal scale (Colenbrander, 2002) and on average participants were capable of accurately verifying 80.46 ± 11.18 written sentences in two minutes, at an average of 1398 ± 193 milliseconds per sentence (as assessed via the Speed and Capacity of Language Processing, SCOLP, test; Baddley, Emslie, and Nimmo-Smith (1992). One participant was excluded from the final analysis for not completing the visual discrimination task as instructed. This participant was observed to repeatedly press the response keys throughout testing even at times when responses were not expected, i.e., no stimuli were present on the screen (final analysed n=16; mean age 21.5 ± 2.07; range 18-25; 8 females).

Procedure

During the visual discrimination threshold task, each trial began with a fixation cross displayed in the centre of the screen for 500ms, followed by a blank screen for 500ms and finally two sets of letter strings and another fixation cross were presented on screen for 2000ms. The letter strings appeared just above and below the fixation cross fixation cross. After the 2000ms expired the screen again went blank until the next trial began (inter-trial interval = 4000ms; see figure 3).

The stimuli consisted of scrambled written versions of three of the five keywords used per trial in experiment 1, an example of keywords used in experiment 1 are: COOKED BEFORE BELL, in experiment 2 these were visually presented as DCOEOK BEROEF LBLE. On an "identical trial" participants would simply see this letter string presented concurrently above and below the central fixation cross. On a "different trial" three of the middle letters were changed in one of the three nonsense words. The first and last letters of all nonsense words were always held constant on different trials so that matching could not rely solely on the initial and final letter. Additionally, all stimuli and fixation crosses were presented using Courier New in font size 60. This is a fixed width font and therefore both sets of letter strings occupied the same horizontal space and thus matching had to rely on more than simple length comparisons.

The study consisted of 120 trials divided up into 30 trials per TMS condition. Of the 30 trials, 15 were identical and 15 were different. On the 15 "different trials" the change occurred five times equally across the first, second and third word. Letters were changed by simply replacing the three relevant letters with the next letter in the English alphabet, for example DCOEOK BEROEF LBLE became DCOEOK BE**SPF**F LBLE. Nonsense letter strings were used in place of real words in order to avoid ceiling effects, thus making an effect due to TMS modulation possible.

In order to make the visual discrimination threshold task as comparable to the speech reception threshold task used in experiment 1, a staircase procedure was again adopted. In the same way that the level of the speech shaped background noise varied adaptively dependent on performance, in the current experiment the contrast level between the background and foreground (i.e., the visually presented text) was varied adaptively akin to the Pelli-Robson contrast sensitivity chart (Pelli & Bex, 2013; Pelli & Robson, 1988). On all trials, the background was black with an RGB value of [0,0,0], on the first trial the letter stings appeared with an RGB value of [0.8, 0.8, 0.8], and therefore appeared as white text on a black background. Correct discrimination resulted in an initial contrast change of +/-0.1. As a result, correct discrimination resulted in a text RGB value of [0.7,0.7,0.7] on the subsequent trial whilst incorrect discrimination would result in a text RGB value of [0.9,0.9,0.9]. This change occurred for the first 10 trials; for trials 11 to 16 contrast changes occurred in steps of 0.05; trials 17 to 25 in steps of 0.025 and 0.001 for trials 26 to 30.

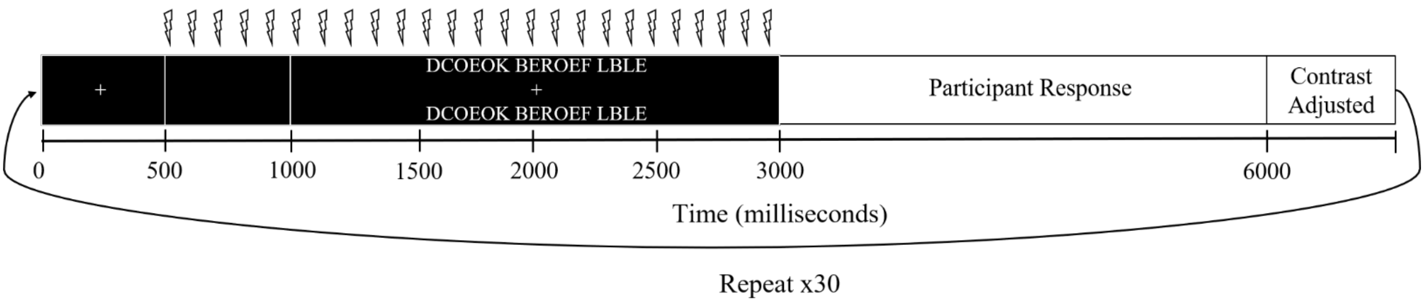

Figure 3- Illustrating the timing of events on an average visual discrimination threshold trial. Repetitive TMS (represented by lightning bolts) start 500ms before the onset of the target visual stimuli. Repetitive TMS and target stimuli offsets occurred concurrently.

As with experiment 1, participants visual discrimination thresholds were computed by taking the mean RGB value of the letter strings for all trials where a reversal occurred (scores closer to zero represent better overall performance). Orders of stimuli list and stimulation sites were counterbalanced across participants. All stimuli lists were pseudo-randomly ordered such that the order of presentation was different between participants but each set of three nonsense letter string ‘sentences’ only appeared once per participant. During pilot testing, it was found that this task incurred a fairly large learning effect, therefore all participants completed 60 practice trials before starting the actual experimental session. No such practice effect was observed for the speech recognition threshold task in experiment 1, as attested via a one-way ANOVA with factor, testing order (first set of sentences presented vs second vs third vs fourth) showing no significant difference in order of sentence presentation, $F(3,45)=1.51$, $p=.224$, $\eta^2=.092$. The TMS stimulator and procedure were identical to those used in experiment 1 with 25 pulses administered per trial at a rate of 10Hz.

MNI-152 structural brain scan

Individual MRI structural scans were not obtained for any participants, instead the MNI-152 brain was used to guide placement of the TMS coil. The procedure changed here because a BrainSight software update provided a method for accurately positioning the coil without collecting individual structural scans. Compared to using frameless stereotaxy based on individual structural scans, the precision of localisation using the average MNI structural brain was estimated to vary by less than 5mm (Rogue Resolutions, personal communication) and thus any inaccuracy in this localisation technique was expected to be small, relative to the induced electrical field of a TMS pulse (Schönfeldt-Lecuona et al., 2005; Thielscher & Kammer, 2004). Both the participant specific anatomical scans of Experiment 1 and the MNI template brain of Experiment 2 contain intrinsic spatial uncertainty from a combination of the spatial normalisation procedure (i.e. use of an averaged MNI coordinate), and the unknowable functional and structural variation between participants. The only feature that differs between both techniques is the ability to adjust for anatomical variations when using participant-specific MRI scans. While such minor adjustments were made for individual anatomical variability in Experiment 1, these adjustments were on the order of millimetres (average change of 1mm in the y-coordinate), and therefore fell within the spatial resolution of TMS (5-10mm). Therefore, while such adjustments were not possible using the MNI structural scan in experiment 2, it does not seem plausible that the use of two different localisation techniques will have substantially affected our results, as the variations associated within either technique were likely below the spatial resolution of TMS. Anecdotally, our experience suggests that the MNI template brain method is just as accurate as using an individual's structural for finding the hand region of the primary motor cortex, and therefore it is reasonable to assume the results are comparable to the procedure used in experiment 1 for stimulation of left or right STG (or vertex). In conjunction with Brainsight 2.3.5 the MNI-152 brain was adapted based on a minimum of five separate estimations of the front-, back-, top-, left- and rightmost points on each participant's head with the MNI brain adapted to meet the measured dimensions. TMS target locations were the same as used in experiment 1: left STG (x = −60, y = −12, z = −6); right STG (x = +62, y = −8, z = −10); vertex (x= 0, y = 0, z= +90) and a no TMS baseline condition. As the MNI-152 brain was fit to the dimensions of each participant's cranium, there was no need to adjust the target coordinates on an individual participant basis (as with experiment 1) and therefore the average coordinates match the target coordinates.

Results

A repeated-measures analysis of variance (ANOVA) was conducted to investigate whether the application of TMS to different anatomical landmarks (no TMS; vertex; left STG; right STG) produced differential effects on participants' ability to discriminate between two nonsense letter strings at varying degrees of visual contrast. No significant main effect of TMS condition was found $F(3,45)=1.08$, $p=.367$, $\eta^2=0.067$, indicating that the performance of the visual discrimination threshold did not differ regardless of location of stimulation. To ensure that no significant differences are masked by an overall non-significant main effect, follow up post-hoc analyses were conducted without any correction for multiple comparisons. All comparisons returned non-significant results (all p's>.06). Therefore, the current stimulation parameters had no significant effect on the visual discrimination threshold performance, suggesting that non-specific disruption such as muscle twitching was not sufficient to impair performance on the visual discrimination threshold task. Note that these results contrast with those of experiment 1, where stimulation of left or right STG disrupted performance on the speech recognition threshold task.

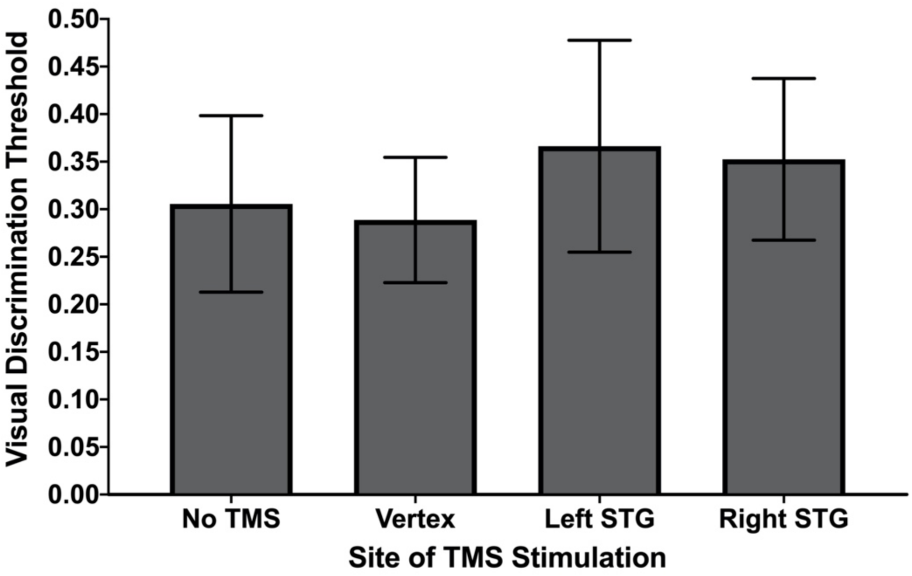

Figure 4 - Depicting the average contrast level (RGB) at the point of a reversal across the four sites of TMS stimulation. Error bars represent 95% confidence intervals.

General Discussion

The aim of the current experiments was to develop our understanding of the role of bilateral superior temporal gyri in processing speech in noise, in doing so we aimed to evaluate the claims made by the unilateral model of Rauschecker and Scott (2009) and the bilateral model of Hickok and Poeppel (2000) by temporarily disrupting left or right STG using repetitive transcranial magnetic stimulation and measuring its impact on participants' ability to perceive speech in noise. The results show that TMS to either the left *or* right superior temporal gyrus reduced participants' ability to recognise speech in noise and thus supports neurobiological models of speech perception that hypothesise bilateral processing in speech perception. These results have ramifications for current and future neurobiological models of speech perception which should acknowledge and subsequently understand the important roles that both hemispheres play.

Whilst a significant effect of TMS was found in experiment 1, no effect of TMS was found in experiment 2. The second experiment used a visual discrimination task to assess whether TMS induced direct innervation of the temporalis muscle (a common side effect of TMS) impaired participants' ability to focus on the SRT task used in experiment 1. The lack of a significant effect in experiment 2 is important as it precludes the possibility that the results of experiment 1 are due to the nonspecific effects of TMS, the parameters for which were identical across experiments. The non-significant result in experiment 2 strongly suggests that participants were able to maintain enough attention despite innervation of facial musculature to complete the task in a valid way, with changes in performance on the speech task being driven by the cortical modulations induced through TMS. This is critically important for the current study and future studies, as it highlights that online TMS designs are appropriate to investigate speech perception. The importance here is highlighted by the results of Andoh and Paus (2011) who have shown that the application of offline TMS results in compensatory modulations in ipsi- and contra-lateral regions of the brain to an extent that the behavioural perturbations induced through TMS can be overcome. When investigating action selection with TMS and fMRI, O'Shea, Johansen-Berg, Trief, Göbel, and Rushworth

(2007) found that these compensatory processes occur within the first four minutes after TMS-induced neural modulation. Therefore, by using an online, as opposed to an offline, repetitive TMS paradigm we were able to establish the immediate impact of the disruption before any (or at least before the majority of) cortical adaptation occurred. These findings most closely approximate the impact of immediate neural trauma to superior temporal regions, and the associated effect on speech perception.

Whilst the difference in speech reception thresholds between bilateral STG and the control conditions in experiment 1 was significant, the overall magnitude of the effect is small. The just noticeable difference (JND) refers to the minimum level by which a stimulus must change before the difference is noticeable. Whilst there is still some disagreement as to the exact JND for speech embedded in noise, it is believed to be roughly two to three decibels (Killion, 2004; McShefferty, Whitmer, & Akeroyd, 2015). This suggests that for a listener to gain any benefit from noise reduction in an acoustic signal, the noise would have to be reduced by a minimum of two decibels. In comparison, the observed difference found in experiment 1 of one to two decibels between the left and right STG compared to the no TMS and vertex condition could be considered minimal in a real-world setting. However, this should be considered as a general limitation of TMS as a research technique as opposed to a limitation of the current results. Whilst the level of cortical modulation in TMS studies can be enough to impair performance allowing causal inferences concerning the role of certain regions on a specific task, the impairment in performance is often reflected in very subtle changes, i.e., hundreds of milliseconds delay in response times or a few percentage points in accuracy (Silvanto & Muggleton, 2008). Therefore, an important point to consider is not the size of the effect in real-world circumstances, but instead whether or not a significant effect occurs in the context of the experimental design (de Graaf & Sack, 2011). In experiment 1, a significant effect of repetitive TMS was found when applied online to the left and right STG regions, and even though the effect is small in real-world terms, it is theoretically important and should be considered in the context of the null effect on all control sites (vertex and no TMS) and the control task (visual discrimination) used in experiment 2.

Despite the equivalent level of disruption caused by the application of TMS to each hemisphere, it is not necessarily inferred that the processes being manipulated across the two hemispheres are equivalent. A symmetrical disruption does not in itself necessitate symmetrical functioning (Obleser et al., 2008; Scott et al., 2000) and several previous studies have provided support in favour of hemispheric asymmetries in speech-related auditory processing. In an fMRI study Wong, Uppunda, Parrish, and Dhar (2008) found that speech embedded in noise resulted in increased activation in bilateral superior temporal gyrus. However, the pattern of activation differed between hemispheres. In the left STG activation continued to increase as the noise became more intense while in the right hemisphere, activation increased from clear speech to the moderate SNR condition but did not increase any more as the noise became even more intense. Despite the selective nature of the right hemisphere change in activation, Wong et al. (2008) found that the degree of individual difference in the right hemisphere activation was positively correlated with performance on a behavioural task in the most extreme listening condition (participants with greater right hemisphere activation performed better on the behavioural task), with no correlation found between behavioural performance and left STG activation. When combined with the results of Wong et al. (2008), the results from experiment 1, suggest that speech perception is a bilateral process with both the left and right hemispheres performing important roles in the process, but the nature of the involvement of each hemisphere is likely different.

In conclusion, the results of the experiments presented here showed a TMS-induced impairment in speech perception after stimulation of both left *and* right temporal lobes, and thus support neurobiological models of speech perception that hypothesise bilateral processing in speech perception. Additionally, no effect of TMS was found under any experimental condition on a task requiring visual perception/discrimination and any potential differences induced by the acoustic noise of discharging the coil were controlled for through use of specialised earphones, thus suggesting that the current results are due to the modulation of cortical processing as opposed to nonspecific effects of online rTMS. These results have ramifications for current and future neurobiological models of speech perception and indicate that such models need to acknowledge the importance of both hemispheres. Finally, these results provide a base upon which future TMS studies can be conducted to investigate the specific roles that each hemisphere plays during successful speech perception.

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